IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Giammona et al. Confirmation No.: 4701

Serial No. : 10/596,267

Filed : February 7, 2007

Art Unit : 1617

Examiner : Browe D.

For : **ANIONIC HYDROGEL MATRICES WITH PH DEPENDENT MODIFIED RELEASE AS DRUG CARRIERS**

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Commissioner for Patents
Alexandria, VA 22313-1450

APPEAL BRIEF UNDER 37 C.F.R. §41.37

This is an appeal from the final rejection of claims 1, 5-15 and 17-19 made in the Final Office Action mailed August 16, 2010 in the referenced application ("Final Office Action"). For the reasons discussed below, Appellants request reversal of the rejections of the claims and allowance thereof.

A Notice of Appeal was filed on November 16, 2010, making the filing of this Appeal Brief timely.

TABLE OF CONTENTS

I. REAL PARTY IN INTEREST

The real party in interest is **Sigma-Tau Industrie Farmaceutiche Riunite S.P.A.** of Rome, Italy, the assignee of record.

II. RELATED APPEALS AND INTERFERENCES

None.

III. STATUS OF THE CLAIMS

Claims 1, 5-15 and 17-19 are currently rejected and are presented on appeal.

Claims 2-4 and 16 have been cancelled.

A copy of the claims presented on appeal is attached in Section VIII, Claims Appendix.

IV. STATUS OF THE AMENDMENTS

An amendment to the claims has been filed on November 2, 2010 subsequent to the Final Rejection of August 16, 2010. For purposes of appeal, the proposed amendment was entered by the Examiner.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

Independent claim 1 recites an anionic hydrogel matrix obtained by chemical reticulation by means of irradiation of polymers suitably derivatised with photoreticulable groups. The photoreticulable groups are derived from the insertion of glycidyl methacrylate and methacrylic anhydride in the side chain of PHEA in the presence of acid monomers.

Support for independent claim 1, as pending, is found on page 4, lines 11-23, page 9, lines 10-19 and from page 13, line 12 to page 15 line 24 of the specification as originally filed.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether claims 1, 5-15 and 17-19 are unpatentable under 35 U.S.C. § 103(a) over Bromberg et al. (U.S. Patent Application Publication No. 20030152623, hereinafter "Bromberg") in view of Blum et al. (U.S. Patent No. 6,294,591, hereinafter "Blum") Giammona et al. (Biochimica et Biophysica Acta, 1999, hereinafter "Giammona") and Cavazza (U.S. Patent No. 6,013,670, hereinafter "Cavazza").

VII. ARGUMENT

Pending claims 1, 5-15 and 17-19 were rejected under 35 U.S.C. § 103(a), for allegedly being unpatentable over Bromberg in view of Blum, Giammona and Cavazza (Final Office Action, page 4).

Appellants discuss below the errors made by the Examiner and how, in view of these errors, the claims do contain subject matter which would not have been rendered obvious by the combination of the cited references.

Independent claim 1 is directed to an anionic hydrogel matrix obtained by chemical reticulation by means of irradiation of polymers suitably derivatised with photoreticulable groups. The photoreticulable groups are derived from the insertion of glycidyl methacrylate (GMA) and methacrylic anhydride (MA) in the side chain of PHEA in the presence of acid comonomers (*e.g.*, page 4, lines 11-23, page 9, lines 10-19 and from page 13, line 12 to page 15 line 24).

Bromberg does not disclose Appellants' invention. Bromberg only provides for a plethora of suitable polymers which do not include the polyaspartamide derivatized polymers presently claimed (*e.g.*, paragraphs [0087]-[0115] for a total of 11 pages).

Thus, one skilled in the art would find no motivation to choose a poly-L-aspartic acid among the long list of components disclosed in Bromberg to modify it as presently claimed with a reasonable expectation of success and without the help of impermissible hindsight. *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007) ("A claimed compound would not have been obvious where it was not obvious to try to obtain it from a broad range of compounds, any one of which could have been selected as the lead compound for further investigation, ….and there was not reasonable expectation of success").

Blum cannot correct Bromberg's deficiencies, because it suffers from the same defects. Namely, Blum only describes that it is possible to form polymers with reactive side group, but it is completely silent with regard to PHEA (*e.g.*, col. 1 line 63 to col. 2 line 3).

Further, Appellants submit that Blum is not a reference analogous to the field of Appellants' endeavor (MPEP § 2141.01(a)). *Agrizap, Inc. v. Woodstream Corp.*, 520 F.3d 1337 (Fed. Cir. 2008).

The court in *Agrizap* held that analogous art is not limited to references in the field of endeavor of the invention, but includes also references that would have been recognized by those of ordinary skill in the art as useful for Applicants' purpose.

However, the facts of the present case are quite different. That is, Blum relates only to polymers known and used to produce radiation-curable coatings, paints, adhesives or impregnating compositions (*e.g.*, col. 1, lines 9-11).

These purposes are not useful at all for Appellants invention which relates to the field of pharmaceutical technology. Thus, Appellants respectfully point out that for this reason only Blum should not be considered a suitable 35 U.S.C. § 103(a) reference against Appellants' claims.

Moreover, Appellants disagree with the Examiner's statement on page 12 of the Final Office Action citing Blum "*the selection of monomers for combination is made in accordance with principles familiar to the skilled workers such that they satisfy the requirements of the envisage application. These requirements may differ greatly*;" (*e.g.*, Blum col. 3, lines 36-39). The Examiner is taking the position that a person of ordinary skill in the pharmaceutical arts would thus readily recognize and be able to take advantage of the relevant teachings the Blum reference affords to the pharmaceutical art.

Appellants respectfully submit that this entire citation of Blum is taken out of context, is incomplete and is incorrect.

Following the Examiner's citation, Blum discloses that "*These requirements may differ greatly; for example, transparent automotive topcoats for metallic finishes are required to have very high resistance to yellowness and weathering, high scratch resistance and good gloss retention coupled with high hardness.*" (*e.g.*, Blum col. 3, lines 39-47).

Accordingly, Appellants assert that on the contrary to the Examiner's conclusions, Blum affords no relevant teachings to the pharmaceutical arts. Nothing in Blum hints to the pharmaceutical arts, and therefore, unlike in *Agrizap*, one skill in the art would not have recognized Blum as been useful for Applicants' purposes and would not have considered its teachings.

Therefore, one skilled in the art of making drugs would not look at the teachings of Blum, who are limited only to the field of making paintings, to learn how to prepare a drug formulation. Thus, for this additional reason, Appellants respectfully submit that Blum cannot be used as a reference to sustain an allegedly obviousness rejection of Appellants' claims and cannot provide for the deficiencies of Bromberg.

Thus, it necessary follows that the Examiner's' comment on page 13 of the Final Office Action (*e.g.*, lines 5-10) also becomes irrelevant. In other words, since Blum cannot be considered as a relevant reference to support a *prima facie* obviousness rejection, it cannot provide for Giammona's missing link either.

Giammona only provides for the synthesis and characterization of new biodegradable hydrogels (*e.g.*, the Abstract). However, Giammona is completely silent with regard to PHEA derivatisable with GMA and MA and to the presence of acid comonomers.

In the Final Office Action, the Examiner responded to Appellants' arguments by saying that "it was already established and disclosed at the time of the present application that PHEA could be photo-crosslinked by insertion of GMA into the side chain and that one skilled in the art would have found obvious to insert MA starting from the teaching of Blum (*e.g.*, Final Office Action, page 13). Appellants respectfully disagree with these conclusions.

As set forth above, Blum cannot be considered a relevant reference to support a *prima facie* obviousness rejection. Thus, Blum cannot provide for any teachings to supply for the deficiencies of Giammona. As such, Appellants respectfully submit that the combination of Bromberg with Blum and Giammona still does not disclose all of the claimed limitations and therefore would not have rendered obvious the claimed subject matter.

It is settled law that obviousness can be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so. *In re Kahn*, 441, F.3d 977, 986, 78 USPQ2d 1329, 1335 (Fed. Cir. 2006). As set forth above, Blum provides no motivation to one skilled in the art to insert MA into PHEA photo-crosslinked by insertion of GMA into the side chains. On the contrary, Blum is not analogous to the field of Appellants' invention and does not provide any useful teaching for the person of skills in the pharmaceutical art.

Second, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, _____, 82 USPQ2d 1385, 1396 (2007). The simple reason that Blum and Giammona could be combined is not enough to render obvious the claimed subject matter because one of ordinary skill in the art would not even have considered Blum as a potential reference to be combined with Giammona.

Moreover, a statement that modifications of the prior art to meet the claimed invention would have been "'well within the ordinary skill in the art at the time the claimed invention was made'" because the references relied upon teach all aspects of the claimed invention were individually known in the art, is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). Thus, the Examiner's statement that it was established and disclosed at the time of the present application that PHEA could be photo-crosslinked by insertion of GMA into the side chain and thus, any person of ordinary skill in the art would find it obvious from the disclosure of Blum to insert MA as well, is not enough to establish a *prima facie* case of obviousness. No objective reasons or motivations have been provided to explain why such teachings should be combined.

Finally, Cavazza is irrelevant with regard to the presently claimed anionic hydrogel matrix composition as recited in claims 1, 5-14. Cavazza only provides for the treatment of chronic inflammatory bowel diseases with lower alkanoyl L-carnitines (*e.g.*, col. 1, lines 6-10). Thus, it cannot render obvious the subject matter of claims 1, 5-14.

Further, as Bromberg, combined with Blum and Giammona would not have rendered obvious the claimed subject matter for the reason set forth above, it is respectfully submitted that they would not have rendered obvious the subject matter of claims 15 and 17-19 as well. Thus, Cavazza, which does not cure the deficiencies of any of the cited references because it suffers from the same defects, would also not have rendered obvious the subject matter of claims 15 and 17-19.

Thus, for all of the reasons set forth above, Appellants respectfully submit that the combination of the cited references would not have rendered obvious the claimed subject matter to one skilled in the art.

Accordingly, the rejection of claims 1, 5-15 and 17-19 under 35 U.S.C. § 103(a) is untenable and improper and should be reversed.

VIII. CLAIMS APPENDIX

1. Anionic hydrogel matrix obtained by chemical reticulation by means of irradiation of polymers suitably derivatised with photoreticulable groups, wherein the photoreticulable groups are derived from the insertion of glycidyl methacrylate (GMA) and methacrylic anhydride (MA) in the side chain of PHEA in the presence of acid comonomers.

5. Matrix according to claim 1, in which the acid comonomer is selected from methacrylic acid or acrylic acid.

6. Matrix according to claim 1, in which the irradiation agents are selected from the group consisting of gamma rays, beta rays and ultraviolet radiation.

7. Matrix according to claim 1, in the form of nanoparticles, microparticles, gels, films, cylinders or sponges, the preferred form being microparticles.

8. Pharmaceutical composition consisting of a matrix according to claim 1 and one or more active ingredients.

9. Composition according to claim 8, containing additionally one or more pharmaceutically acceptable excipients.

10. Composition according to claim 9, in which the excipients are selected from the group consisting of bioadhesives, chitosans, polyacrylamides, natural or synthetic rubbers and acrylic acid polymers.

11. Composition according to claim 8, in which said active ingredients are selected from the group consisting of

- analgesic agents, such as acetaminophen, phenacetin and sodium salicylate;

- antitussive agents, such as dextromethorphan and codeine phosphate;

- bronchodilators, such as albuterol and procaterol;
- antipsychotics, such as haloperidol and chlorpromazine;
- antihypertensive agents and coronary dilators, such as mono- and dinitrate isosorbide and captopril;
- selective 6-2 antagonists, such as salbutamol, terbutaline, ephedrine, and orciprenaline sulphate;
- calcium antagonists, such as nifedipine, nicardipine, diltiazem and verapamil;
- antiparkinson drugs, such as pergolide, carpidopa and levodopa;
- hormones;
- non-steroidal and steroidal anti-inflammatory drugs, such as ketoprofene, ibuprofene, diclofenac, diflunisal, piroxicam, naproxene, kerotolac, nimesulide, budesonide, tiaprofenic acid, mesalazine (5-aminosalicylic acid) cortisone, hydrocortisone, betamethasone and prednisone;
- antihistamines, such as terfenadine and loratadine;
- antidiarrhoeal and intestinal anti-inflammatory agents such as loperamide, 5-aminosalicylic acid, olsalazine, sulfasalazine and budenoside;
- spasmolytics, such as octylonium bromide;
- anxiolytics, such as chlordiazepoxides, oxazepam, medazepam, alprazolam, donazepam and lorazepam;
- oral antidiabetic agents, such as glipizide, methformin, phenphormin, gliclazide and glibenclamide;
- cathartics, such as bisacodil and sodium picosulphate;
- antiepileptic agents, such as valproate, carbamazepine, phenytoin and gabapentin;

- anticancer agents;
- disinfectants of the oral cavity or antimicrobials, such as benzalkonium chloride, cetylpyridinium chloride or tibezonium iodide, and a number of aminoderivatives such as benzidamine and chlorhexidine as well as their salts and derivatives;
- sodium fluoride;
- cardioactive agents;
- antihistamines;
- L-carnitine and/or one or more alkanoyl L-carnitines, or one of their pharmaceutically acceptable salts.

12. Composition according to claim 11, in which the alkanoyl, straight or branched, has 2-6 carbon atoms, and is selected from the group consisting of acetyl, propionyl, butyryl, valeryl or isovaleryl L-carnitine.

13. Composition according to claim 11, in which said pharmaceutically acceptable salt of L-carnitine or of the alkanoyl L-carnitines is selected from the group consisting of chloride, bromide, orotate, aspartate, acid aspartate, acid citrate, magnesium citrate, phosphate, acid phosphate, fumarate and acid fumarate, magnesium fumarate, lactate, maleate, and acid maleate, oxalate, acid oxalate, pamoate, acid pamoate, sulphate, acid sulphate, glucose phosphate, tartrate and acid tartrate, glycerophosphate, mucate, magnesium tartrate, 2-amino-ethane sulphonate, magnesium 2-amino-ethane sulphonate, methane sulphonate, choline tartrate, trichloroacetate, and trifluoroacetate.

14. Composition according to claim 8 for oral use.

15. Method of treating a patient or an animal in need thereof comprising administering the composition according to claim 8.

17. Method according to claim 15 wherein said patient or animal in need thereof suffers from cardiovascular diseases, tumors, central and peripheral nervous system diseases or intestinal disease.

18. Method according to claim 17, in which the active ingredient useful for the treatment of chronic intestinal disease is propionyl L-carnitine.

19. Method according to claim 15, in which said composition can be administered by the parenteral or vaginal routes.

IX. EVIDENCE APPENDIX

None.

X. RELATED PROCEEDINGS APPENDIX

None.

FEES

Payment by credit card in the amount of Five Hundred Forty Dollars ($540.00) is being concurrently made with the filing of this paper to cover the fee set forth in 37 C.F.R. §41.20(b)(2) for a large entity.

It is believed that no fees other than those paid concurrently are due in connection with the filing of this paper. However, should it be deemed that any other fee is due in connection with this paper, authorization is hereby given to charge such fee to Deposit Account No. 02-2275.

Respectfully submitted

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